REMARKS

Claims 5, 9-16, 19-23, 26 and 30-64 are pending and under examination in the subject application. Claims 5, 26, 32, 33, 39, 54, 57, 58 and 59 have been amended above. Support for the amendments can be found throughout the application. In particular, support for the amendment to claims 5, 26, 32, 33, 39, 54, 57 and 58 can be found at, for example, page 7, lines 8-10. Claim 59 has been amended to correct an informality as suggested in the Office Action. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicant has review the rejections set forth in the Office Action mailed July 14, 2004, and respectfully traverse all grounds for the reasons that follow.

Rejections Under 35 U.S.C. § 102

Claims 5, 13, 32, 39, 45 and 57 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Barany et al., U.S. Patent No. 6,027,889. The Office maintains that Barany et al. describe the detection of nucleic acid sequence differences using coupled ligase detection and polymerase chain reaction (PCR) and further alleges that Barany et al. describe probes having distinct first through fifth portions as recited by the claims. An annotated version of Figure 12 is asserted to show the five distinct portions. The Examiner also alleges that the claims do not require an adapter sequence which spans a ligation junction.

The claims are directed to a method of determining the identification of a nucleotide at a detection position in a target sequence. The method includes hybridizing a first and second ligation probe to first and second target domains of a target sequence. The first ligation probe consists of a first portion containing an upstream universal priming site (UUP) and a second portion containing a first target specific sequence. The second ligation probe consists of a third portion containing a downstream universal priming site (DUP) and a fourth portion consisting of a second target specific sequence. Finally, at least one of the first or second ligation probes contains a fifth portion consisting of an adapter sequence. Therefore, the claims specify different elements within the probes and a correspondence to different portions within the probes. The five portions alleged to be shown in Figure 12 have been annotated to arbitrarily divide at most four discrete portions into a five arbitrary portions. Accordingly, the claims cannot be

anticipated by Barany et al. because Barany et al. describes at most only four portions in the probes relied on by the Office.

As pointed out previously, a further distinction between Barany et al. and the claimed invention is that the purported adapters described by Barany et al. appear to correspond to a region distinct from the adapters of the claimed probes. The adapters described by Barany et al. appear to correspond to a region within a target sequence, and more particularly, the adapters described by Barany et al. appear to correspond to a sequence that spans a ligation junction (see, for example, Office Action mailed January 29, 2003, pages 4-5, and Applicants' previous response at page 18). Therefore, and in contrast to the statement in the Office Action, it is Barany et al. that describe an adapter sequence that spans a ligation junction rather than Applicants' claimed invention.

In light of the claims reciting that the probes contain a fifth portion corresponding to an adapter sequence that is distinct from the first through fourth portions of the claimed ligation probes and in light of the description in the specification specifying that an adapter sequence can differ from the target sequence, Applicants maintain that the claims cannot be anticipated by Barany et al.. Nevertheless, to further prosecution of this application, Applicants have amended claims 5, 32, 39 and 57 to recite that the adapter sequence is specific to the claimed capture probe on the array and distinct from the target sequence. Accordingly, this ground of rejection is moot and withdrawal is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 14-16, 34, 46-48 and 60 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Walt et al., U.S. Patent No. 6327,410. The Office concedes that Barany et al. does not disclose the array as claimed but maintains that one skilled in the art would have been motivated to use the array described by Walt et al. because the replacement of one array type with another type would not change the steps of the experiment. The Office further alleges that its burden has been met and relies on the arguments above with respect to the § 102(e) rejection over Barany et al., asserting that all components of the claimed ligation probes have been described.

Claims 14-16 and 34 depend from independent claims 5, 26, 32 or 33. These independent claims now recite that the adapter portion of a ligation probe corresponding to an adapter sequence is distinct from either of the first through fourth portions of the claimed ligation probes and further that the adapter sequence is specific to a capture probe on the claimed array and distinct from a target sequence. As described above, Applicants have claimed distinct portions of the claimed ligation probes which are absent from the purported description in Barany et al. and distinct from the arbitrary delineation in the Office's annotation of Figure 12. Further, the cited references neither provide a suggestion or motivation to identify a nucleotide at a detection position in a target sequence using a fifth portion consisting of an adapter sequence that is specific to a capture probe and distinct from a target sequence. Absent such a suggestion or motivation, the claims cannot be obvious over the cited art.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03.

Applicants respectfully submit that the Office has not established a *prima facie* case of obviousness, at least because all the components of the claimed ligation probes are neither taught or suggested by the cited art. As described above, the pending claims recite ligation probes containing a fifth portion, distinct from target-specific portions and specific to a capture probe on an array. The cited references at least do not teach or suggest a ligation probe containing these elements. For example, Barany et al. purports to describe an adapter oligonucleotide that corresponds to a nucleotide sequence across the ligation junction. Because the ligation junction corresponds to a target-specific sequence, the description in Barany et al. do not teach or suggest an adapter portion distinct from other portions as claimed. In the absence of a teaching or suggestion in the cited references of each of the components of the claimed ligation probes, the Office has not established a *prima facie* case of obviousness of any of the claims under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Independent claims 26, 33, 45, 54, 58 and claims 10, 13, 19-22, 31, 35, 42, 49-52, 56, 59 and 61 depending therefrom stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over

Zhang et al, U.S. Patent No. 5,876,924, in view of Barany et al. The Office asserts that Zhang et al. describes two oligonucleotide probes, Capture/Amp-probe-1 and Amp-probe-2, hybridized adjacently on a target nucleic acid which contain five distinct portions and alleges that one skilled in the art would have been motivated to replace the ligation method of Zhang et al. with that described by Barany et al. because it would not change the result. An annotated Figure 7 from Zhang et al. has been supplied in support that the probes of Zhang et al. describe five distinct portions. In addition to alleging that that the Office has satisfied its burden, the Office also maintains its reliance on the assertion that there is no change in the basic principle or design between the two methods described in the cited references.

As with the previous rejections over Barany et al. under §102 or Barany et al. in view of Walt under §103, the Office similarly contends that Zhang et al. describes a probe that contains five distinct portions, including an adapter sequence. In this regard, the Office states that the "domain of AMP-PROBE-2 is considered to have two parts: UUP and adapter sequences" (emphasis added). However, Zhang et al. fails to describe an adapter sequence. Moreover, and as with the rejection above, the annotation of Figure 7 appears to be arbitrary because a pair of probes having at most four delineated segments randomly divides one of the segments into two portions. Such an arbitrary division is neither taught or suggested in Zhang et al. In contrast, the claimed ligation probes claim a fifth portion containing an adapter sequence that is specific to a capture probe and distinct from a target sequence.

For the reasons set fourth above, neither Zhang et al. alone, or Zhang et al. in view of Barany et al., teach or suggest a first and a second ligation probe having the five portions as claimed. Accordingly, the cited references fail to teach or suggest all the elements of the claimed invention and cannot provide a basis for a *prima facie* case of obviousness.

Further, there is similarly no motivation to combine the cited art references. If the proposed modification or combination of the cited art would change the principle operation of the art being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 19S9). The Office Action appears to assert that the combination would not alter the principle operation allegedly because both have the common method step of directed to ligation chain reaction.

Reliance on a ligation step for alleging that the principle operation is unchanged fails to recognize that the alleged combination would require substantial reconstruction and redesign of the elements shown in the primary reference to Zhang et al. as well as a change in the basic principle under which Zhang et al. was designed to operate. The ligation steps of Barany et al. and Zhang et al. operate at different steps and apply different hybridization characteristics. For example, the hybridization specificity required to detect an amplification product (Barany et al.) differs from the hybridization specificity required to detect a target sequence (Zhang et al.). As such, the ligation step performs different and separate functions in each method within the cited references.

In light of the above remarks, Applicants maintain that the cited references to Zhang et al. in view of Barany et al. fail to teach or suggest all the elements of the claims and fail to provide a motivation to combine. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 11, 12, 43 and 44 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Zhang et al. in view of Barany et al. as applied to above and further in view of Gebeyehu et al., U.S. Patent No. 4,921,805. Briefly, Gebeyehu et al. is alleged to describe an intercalator attached to a bead to separate non-hybridized probes from hybridized probes as claimed. Similarly, claims 9, 23, 30, 41, 53, and 55 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Zhang et al. in view of Barany et al., as applied above, and further in view of Seradyn Particle Technology. Claims 37 and 63 also stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Zhang et al., in view of Barany et al., and further in view of Monforte et al., U.S. Patent No. 5,830,655. Claims 36 and 62 stand rejected under 35 U.S.C. § 103(a) over the above combination of references and further in view of Brown et al., U.S. Patent No. 5,807,522, whereas claims 38 and 64 stand rejected under 35 U.S.C. § 103(a) over the combination of Zhang et al, in view of Barany et al. and Monforte et al. and further in view of Johnson et al.

All of the above claims depend from one or more of the independent claims 5, 26, 32, 33, 39, 54, 57 and 58. Accordingly, the dependent claims contain all the limitations of the base claims from which they depend. As set fourth above, neither Barany et al. in view of Walt nor

Zhang et al. in view of Barany et al. provide all the elements of the claimed invention or a motivation to combine the respective references. Accordingly, the independent claims are unobvious over the cited combination of references. The above tertiary references are cited allegedly for describing a further element found within the dependent claims. Because the cited art fails to describe each and every element of the claimed invention and because the tertiary references are directed to further elements within the dependent claims, the citations to Gebeyehu et al., Seradyn Particle Technology, Monforte et al. or Johnson et al. cannot cure the deficiencies of the primary and secondary references. Accordingly, the cited art cannot teach or suggest each and every element of the claimed invention and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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